

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|--|-----------|---|
| (51) International Patent Classification ⁷ : A61K 35/00 | A1 | (11) International Publication Number: WO 00/69448 (43) International Publication Date: 23 November 2000 (23.11.00) |
|--|-----------|---|

(21) International Application Number: PCT/US00/12875
(22) International Filing Date: 11 May 2000 (11.05.00)
(30) Priority Data:
60/134,344 14 May 1999 (14.05.99) US

(71) Applicant (for all designated States except US): HENRY FORD
HEALTH SYSTEM [US/US]; 1 Ford Place, 4B, Detroit, MI
48202-3450 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): LI, Yi [US/US]; 7046
Pittsford Drive, Canton, MI 48187 (US). CHOPP, Michael
[US/US]; 28415 Brooks Lane, Southfield, MI 48034 (US).

(74) Agents: KOHN, Kenneth, I. et al.; Kohn & Associates, Suite
410, 30500 Northwestern Highway, Farmington Hills, MI
48334 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG,
BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE,
ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE,
LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT,
BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

*Before the expiration of the time limit for amending the
claims and to be republished in the event of the receipt of
amendments.*

(54) Title: BONE MARROW TRANSPLANTATION FOR TREATMENT OF STROKE

(57) Abstract

There is provided a treatment for patients suffering from neurodegenerative disease or neural injury including the steps of transplanting cultured bone marrow cells into the spinal cord or brain or injecting intravascularly bone marrow cells of a patient in need. Also provided is a method of activating the differentiation of neural cells in an injured brain including the steps of transplanting bone marrow cells adjacent to the injured brain cells and activating the endogenous central nervous system stem cells to differentiate into neurons. A method of treating injured brain or spinal cord cells is also provided including the steps of transplanting bone marrow cells near the injured brain cells and generating new neurons at the location of transplantation. A method of treating injured brain or spinal cord cells with a composite of MSCs and neurospheres.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | | | TR | Turkey |
| BG | Bulgaria | HU | Hungary | ML | Mali | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MN | Mongolia | UA | Ukraine |
| BR | Brazil | IL | Israel | MR | Mauritania | UG | Uganda |
| BY | Belarus | IS | Iceland | MW | Malawi | US | United States of America |
| CA | Canada | IT | Italy | MX | Mexico | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NE | Niger | VN | Viet Nam |
| CG | Congo | KE | Kenya | NL | Netherlands | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NO | Norway | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | NZ | New Zealand | | |
| CM | Cameroon | | Republic of Korea | PL | Poland | | |
| CN | China | KR | Republic of Korea | PT | Portugal | | |
| CU | Cuba | KZ | Kazakstan | RO | Romania | | |
| CZ | Czech Republic | LC | Saint Lucia | RU | Russian Federation | | |
| DE | Germany | LI | Liechtenstein | SD | Sudan | | |
| DK | Denmark | LK | Sri Lanka | SE | Sweden | | |
| EE | Estonia | LR | Liberia | SG | Singapore | | |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/12875

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 35/00

US CL :424/93.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| A | US 5,750,376 (WEISS et al.) 12 May 1998, entire document. | 1-4 |
| A | US 5,690,927 (MAJOR et al.) 25 November 1997, entire document. | 1-4 |
| A | JACKOWSKI et al. Neural injury repair: hope for the future as barriers to effective CNS regeneration become clearer. British J. Neurosurgery. 1995. Vol. 9, pages 303-317, entire document. | 1-4 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | |
|---|--|
| * Special categories of cited documents: | *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| *A* document defining the general state of the art which is not considered to be of particular relevance | *X* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| *E* earlier document published on or after the international filing date | *Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *G* document member of the same patent family |
| *O* document referring to an oral disclosure, use, exhibition or other means | |
| *P* document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

27 JULY 2000

Date of mailing of the international search report

19 SEP 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ANNE-MARIE BAKER, PH.D.

Telephone No. (703) 308-0196

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

WEST

Dialog (file: medicine)

search terms: transplant?, bone(w)marrow, cell?, brain, spin?, neuron, neurosphere, mesenchymal(w)stem(w)cell, neural, neurodegenerative, stroke, injury

EXPRESS MAIL Mailing Label Number

5-11-00

I hereby certify that this paper or fee is being deposited with the United States Postal Service at the Post Office To Addressed service under 39 U.S.C. 1101 in the date indicated above, and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20531.

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

| | |
|--|--|
| For receiving Office use only | |
| International Application No. | |
| International Filing Date | |
| Name of receiving Office and "PCT International Application" | |

Applicant's or agent's file reference (if desired) (12 characters maximum) 1059.00042

| | |
|---|--|
| Box No. I TITLE OF INVENTION | |
| BONE MARROW TRANSPLANTATION FOR TREATMENT OF STROKE | |
| Box No. II APPLICANT | |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) | |
| HENRY FORD HEALTH SYSTEM One Ford Place, Suite 4B Detroit, Michigan 48202-3450 United States of America | |
| <input type="checkbox"/> This person is also inventor. Telephone No. Facsimile No. Teleprinter No. | |
| State (that is, country) of nationality: US | State (that is, country) of residence: US |
| This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input checked="" type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box | |
| Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S) | |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) | |
| LI, Yi 7046 Pittsford Drive Canton, Michigan 48187 United States of America | |
| This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.) | |
| State (that is, country) of nationality: US | State (that is, country) of residence: US |
| This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box | |
| <input checked="" type="checkbox"/> Further applicants and/or (further) inventors are indicated on a continuation sheet. | |
| Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE | |
| The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: <input checked="" type="checkbox"/> agent <input type="checkbox"/> common representative | |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) | |
| KOHN, Kenneth I. RINALDO, Amy E. KOHN & ASSOCIATES 30500 Northwestern Highway, Suite 410 Farmington Hills, Michigan 48334 United States of America | |
| Telephone No. 248-539-5050 Facsimile No. 248-539-5055 Teleprinter No. | |
| <input type="checkbox"/> Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent. | |

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

CHOPP, Michael
28415 Brooks Lane
Southfield, Michigan 48034
United States of America

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

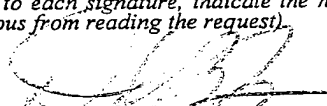
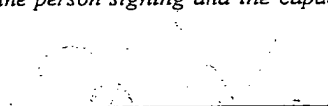
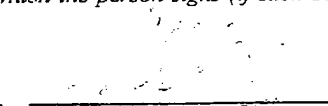
- | | |
|--|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MA Morocco |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BR Brazil | |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CR Costa Rica | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DM Dominica | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> TZ United Republic of Tanzania |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IN India | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IS Iceland | |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> ZA South Africa |
| | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KR Republic of Korea | |
| <input checked="" type="checkbox"/> KZ Kazakhstan | |
| <input checked="" type="checkbox"/> LC Saint Lucia | |
| <input checked="" type="checkbox"/> LK Sri Lanka | |

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☐

☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time

| | | | | |
|---|----------------------------------|---|--|--|
| Box No. VI PRIORITY CLAIM | | <input type="checkbox"/> Further priority claims are indicated in the Supplemental Box. | | |
| Filing date of earlier application (day/month/year) | Number of earlier application | Where earlier application is: | | |
| | | national application: country | regional application: regional Office | international application: receiving Office |
| item (1) 14 May 1999 (14.05.99) | 50/134,344 | | | |
| item (2) | | | | |
| item (3) | | | | |
| <input checked="" type="checkbox"/> The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): 1 | | | | |
| <small>* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(iii)). See Supplemental Box.</small> | | | | |
| Box No. VII INTERNATIONAL SEARCHING AUTHORITY | | | | |
| Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): | | Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year) Number Country (or regional Office) | | |
| ISA/JS | | | | |
| Box No. VIII CHECK LIST: LANGUAGE OF FILING | | | | |
| This international application contains the following number of sheets: request : 4 description (excluding sequence listing part) : 27 claims : 1 abstract : 1 drawings : 11 sequence listing part of description : _____ Total number of sheets : 44 | | This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input type="checkbox"/> separate signed power of attorney 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input checked="" type="checkbox"/> other (specify): Transmittal Letter, Acknowledgment Postcard | | |
| Figure of the drawings which should accompany the abstract: | | Language of filing of the international application: English | | |
| Box No. IX SIGNATURE OF APPLICANT OR AGENT | | | | |
| Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request). | | | | |
|  David B. Lee, Senior Corporate Counsel, Henry Ford Health System | |  Yi Li | | |
| | |  Michael Chopp | | |

| | | |
|---|--|--|
| For receiving Office use only | | 2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received: |
| 1. Date of actual receipt of the purported international application: | | |
| 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: | | |
| 4. Date of timely receipt of the required corrections under PCT Article 11(2): | | |
| 5. International Searching Authority (if two or more are competent): ISA/ | 6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid. | |

| | |
|---|-----------------------------------|
| Date of receipt of the record copy by the International Bureau: | For International Bureau use only |
|---|-----------------------------------|

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's
file reference

1059.00042

Applicant

HENRY FORD HEALTH SYSTEM

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE 240.00 T

2. SEARCH FEE 700.00 S

International search to be carried out by US

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 44 sheets.

first 30 sheets 427.00 b1

14 x \$10.00 = 140.00 b2

remaining sheets additional amount

Add amounts entered at b1 and b2 and enter total at B 567.00 B

Designation Fees

The international application contains all designations.

8 x 92.00 = 736.00 D

number of designation fees payable (maximum 8) amount of designation fee

Add amounts entered at B and D and enter total at I 1,303.00 I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT (if applicable) 15.00 P

5. TOTAL FEES PAYABLE 2,258.00

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

TOTAL

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge
deposit account (see below)

☐ bank draft

☐ coupons

☒ cheque

☐ cash

☐ other (specify):

☐ postal money order

☐ revenue stamps

DEPOSIT ACCOUNT AUTHORIZATION (this mode of payment may not be available at all receiving Offices)

The RO/ US ☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☒ (this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

11-1449

11 May 2000

Deposit Account No.

Date (day/month/year)

Signature

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 30 OCT 2001

WIPO

PCT

| | | |
|---|--|---|
| Applicant's or agent's file reference 1059.00042 | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/US00/12875 | International filing date (day/month/year) 11 MAY 2000 | Priority date (day/month/year) 14 MAY 1999 |
| International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 35/00 and US Cl.: 424/93.1 | | |
| Applicant HENRY FORD HEALTH SYSTEM | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 3 sheets.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| | |
|--|--|
| Date of submission of the demand 15 NOVEMBER 2000 | Date of completion of this report 20 SEPTEMBER 2001 |
| Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 | Authorized officer Anne-Marie Baker, Ph.D. |
| Facsimile No. (703) 305-3230 | Telephone No. (703) 308-0196 |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/12875

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed☒ the description:

pages 1-27, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

☒ the claims:

pages 28, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of

☒ the drawings:

pages 1-17, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

☒ the sequence listing part of the description:

pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
☒ the claims, Nos. NONE
☒ the drawings, sheets/fig. NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/12875

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

| | | |
|-------------------------------|--------------------|-----|
| Novelty (N) | Claims <u>1-4</u> | YES |
| | Claims <u>NONE</u> | NO |
| Inventive Step (IS) | Claims <u>1-4</u> | YES |
| | Claims <u>NONE</u> | NO |
| Industrial Applicability (IA) | Claims <u>1-4</u> | YES |
| | Claims <u>NONE</u> | NO |

2. citations and explanations (Rule 70.7)

Claims 1-4 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest transplanting cultured bone marrow cells or a composite of mesenchymal stem cells and neurospheres into the brain or spinal cord to treat a patient. Thus, the prior art does not teach or suggest the claimed invention.

_____ NEW CITATIONS _____
NONE

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

To: KENNETH I. KOHN
KOHN & ASSOCIATES
30500 NORTHWESTERN HIGHWAY
SUITE 410
FARMINGTON HILLS MI 48334

Date of Mailing
(day/month/year)

25 OCT 2001

Applicant's or agent's file reference

1059.00042

IMPORTANT NOTIFICATION

International application No.

PCT/US00/12875

International filing date (day/month/year)

11 MAY 2000

Priority Date (day/month/year)

14 MAY 1999

Applicant

HENRY FORD HEALTH SYSTEM

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

Anne-Marie Baker, Ph.D.

Telephone No. (703) 308-0196

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|---|---|---|
| Applicant's or agent's file reference 1059.00042 | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/US00/12875 | International filing date (day/month/year) 11 MAY 2000 | Priority date (day/month/year) 14 MAY 1999 |
| International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 35/00 and US Cl.: 424/93.1 | | |
| Applicant HENRY FORD HEALTH SYSTEM | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

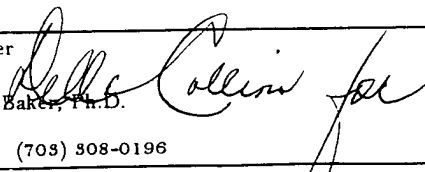
2. This REPORT consists of a total of 3 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| | |
|--|--|
| Date of submission of the demand 15 NOVEMBER 2000 | Date of completion of this report 20 SEPTEMBER 2001 |
| Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 | Authorized officer  Anne-Marie Baker, Ph.D. |
| Facsimile No. (703) 305-3230 | Telephone No. (703) 308-0196 |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/12875

I. Basis of the report

1. With regard to the **elements** of the international application:*☒ the international application as originally filed☒ the description:

pages 1-27 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the claims:

pages 28 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the drawings:

pages 1-17 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the sequence listing part of the description:

pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:☐ contained in the international application in printed form.☐ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.4. ☒ The amendments have resulted in the cancellation of:☒ the description, pages NONE☒ the claims, Nos. NONE☒ the drawings, sheets/fig NONE5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/12875

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)

Claims 1-4 YESClaims NONE NO

Inventive Step (IS)

Claims 1-4 YESClaims NONE NO

Industrial Applicability (IA)

Claims 1-4 YESClaims NONE NO

2. citations and explanations (Rule 70.7)

Claims 1-4 meet the criteria set out in PCT Article 35(2)-(4), because the prior art does not teach or fairly suggest transplanting cultured bone marrow cells or a composite of mesenchymal stem cells and neurospheres into the brain or spinal cord to treat a patient. Thus, the prior art does not teach or suggest the claimed invention.

____ NEW CITATIONS ____
NONE

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: KENNETH I. KOHN
KOHN & ASSOCIATES
30500 NORTHWESTERN HIGHWAY
SUITE 410
FARMINGTON HILLS MI 48334

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

| | |
|---|--|
| Applicant's or agent's file reference 1059.00042 | Date of Mailing (day/month/year) 19 SEP 2000 |
| International application No. PCT/US00/12875 | International filing date (day/month/year) 11 MAY 2000 |
| Applicant HENRY FORD HEALTH SYSTEM | |

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.
Filing of amendments and statement under Article 19:
 The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):
When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.
Where? Directly to the International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland
 Facsimile No.: (41-22) 740.14.35
 For more detailed instructions, see the notes on the accompanying sheet.
2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
 - ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
 - ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.
4. **Further action(s):** The applicant is reminded of the following:
 - Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.
 - Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).
 - Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized Officer
ANNE-MARIE BAKER, PH.D.

Telephone No. (703) 308-0196

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|---|--|
| Applicant's or agent's file reference 1059.00042 | FOR FURTHER ACTION | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |
| International application No. PCT/US00/12875 | International filing date (day/month/year) 11 MAY 2000 | (Earliest) Priority Date (day/month/year) 14 MAY 1999 |
| Applicant HENRY FORD HEALTH SYSTEM | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☐ Certain claims were found unsearchable (See Box I).
3. ☐ Unity of invention is lacking (See Box II).
4. With regard to the title,
- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is Figure No. _____
- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.
- ☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/12875

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 35/00

US CL :424/93.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| A | US 5,750,376 (WEISS et al.) 12 May 1998, entire document. | 1-4 |
| A | US 5,690,927 (MAJOR et al.) 25 November 1997, entire document. | 1-4 |
| A | JACKOWSKI et al. Neural injury repair: hope for the future as barriers to effective CNS regeneration become clearer. British J. Neurosurgery. 1995. Vol. 9, pages 303-317, entire document. | 1-4 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | |
|---|--|
| * Special categories of cited documents: | *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| *A* document defining the general state of the art which is not considered to be of particular relevance | *X* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| *E* earlier document published on or after the international filing date | *Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *G* document member of the same patent family |
| *O* document referring to an oral disclosure, use, exhibition or other means | |
| *P* document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

27 JULY 2000

Date of mailing of the international search report

19 SEP 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ANNE-MARIE BAKER, PH.D.

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/12875

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

WEST

Dialog (file: medicine)

search terms: transplant?, bone(w)marrow, cell?, brain, spin?, neuron, neurosphere, mesenchymal(w)stem(w)cell,
neural, neurodegenerative, stroke, injury

PATENT COOPERATION TREATY

PCT
NOTIFICATION OF ELECTION
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

| | |
|---|---|
| Date of mailing (day/month/year) 22 January 2001 (22.01.01) | Applicant's or agent's file reference 1059.00042 |
| International application No. PCT/US00/12875 | Priority date (day/month/year) 14 May 1999 (14.05.99) |
| International filing date (day/month/year) 11 May 2000 (11.05.00) | |
| Applicant LI, Yi et al | |

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
15 November 2000 (15.11.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

BEST AVAILABLE COPY

| | |
|---|---|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35 | Authorized officer Henrik Nyberg Telephone No.: (41-22) 338.83.38 |
|---|---|